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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/828,354	04/21/2004	Michael R. Johnson	251546US96DIV	6696

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EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/828,354	JOHNSON, MICHAEL R.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *82-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *82-96,98,100-103,105,106,108-115 and 118* is/are rejected.

7)☒ Claim(s) *97, 99, 104, 107, 116 and 117* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *21Apr04,15Mar06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Amendment

Applicant's preliminary amendment filed 21 April 2004 and 22 November 2004 have been entered.

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 82-96, 98, 100-103, 105, 106, 108-115 and 118 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 15, 16, 21, 34 and 35 of copending Application No. 10/920,484. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims of the copending application are drawn to a method of reducing risk of infection from pathogens, comprising administering a therapeutically effective amount of a sodium channel blocker.

One of the sodium channel blockers specified in claim 16, which depends from claim 15, which in turn depends from claim 1 of the copending application is the same compound specified in instant claim 109 (the pyridine ring-containing specie). Similarly, one of the sodium channel blockers specified in claim 35 of the copending application, which depends from claim 34 of the copending application, which in turn depends from claim 21 thereof is the same compound specified in instant claim 109 (the pyridine ring-containing specie). Claim 1 of the copending application is drawn to a prophylactic treatment method comprising administering a prophylactically effective amount of a sodium channel blocker or a pharmaceutically acceptable salt thereof to an individual in need of prophylactic treatment against infection or disease from one or more airborne pathogens. Claim 21 of the copending application is drawn to a prophylactic treatment method for reducing the risk of infection, comprising administering a sodium channel blocker to the lungs of the human who may be at risk for infection.

The species common to both the instant application and the copending application renders the claims not patentably distinct; if the claims of the copending application were prior art, they would anticipate the instant claims.

The methods according to the claims of the copending application are not patentably distinct from the claims of the instant application, drawn to chemical compounds *per se*, because those methods require the compound according to instant claim 109, which compound is also embraced by instant claims 82-96, 98, 100-103, 105, 106, 108-114, and is one of the preferred active ingredient compounds in the composition according to instant claim 115. A medical treatment method, as specified in the claims of the copending application, requires a pharmaceutical composition. The method according

to instant claim 118, a method of blocking sodium channels, is inherent in the methods according claims of the copending application because a compound's pharmacological properties cannot be divorced from the compound itself. In practicing the methods of the copending application, one of ordinary skill would actually be practicing the method according to instant claim 118 as well, because the compounds are sodium channel blockers. Section [0104] of the specification of the copending application teaches that the infection-reducing properties of the compounds specified in the methods according to claims 16 and 35 thereof are due to sodium channel-blocking activity.

There is ordinarily no patentable distinction between compositions of matter and methods. Hence, in the absence of a Terminal Disclaimer, an obviousness-type Double Patenting rejection may be made. See *In re Boylan,* 157 USPQ 370 [The patent had a composition of matter and a method of making it; the application had the method of use]; Ex parte MacAdams, 206 USPQ 445 [The patent had a composition of matter; the application had the method of use]; *Geneva Pharmaceuticals Inc. v. GlaxoSmithKline PLC*, 68 USPQ2d 1865 (CA FC 2003) [The earlier patent was drawn to method of use, the later three patents, held invalid in "Geneva II" were drawn to somewhat narrower versions of the composition of matter]; *Mosler Safe & Lock Co. v. Mosler, Bahmann & Co.*, 127 U.S. 354, 21 8 S.Ct. 1148 (1888) [the first patent was of an article; the second patent, held invalid, was for a method of making it].

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

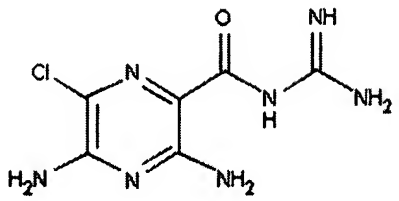
Claims 97, 99, 104, 107, 116 and 117 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Limitations posed by the objected claims are not specified in the claims of the copending application over which an obviousness type double patenting rejection has been made, *supra*. The specification of the copending application does not teach the additional active ingredients in the compositions according to instant claims 116 and 117 either.

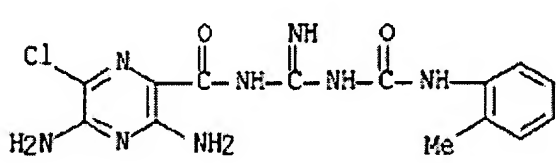
Should applicant file an appropriate Terminal Disclaimer over copending application serial number 10/920,484, the instant application would be in condition for allowance, pending the results of an updated search conducted by the undersigned examiner.

The following is an examiner's statement of reasons for allowance:

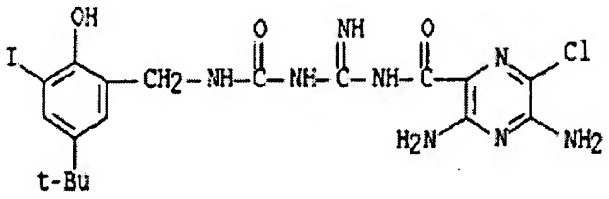
Compounds according to the instant claims are not known from the prior art, nor is there any teaching in the prior art which would render it obvious to make such compounds. Thus, the compositions and method according to the present invention are novel and similarly unobvious. Formula (I) compounds according to the instant claims are based on a core structural motif which is derived from the sodium channel blocking diuretic drug commonly known as "amiloride," which is known from US 3,313,813 (Cragoe, Jr.). Amiloride has the structure shown:



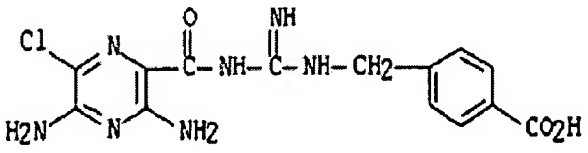
Derivatives of amiloride have been reported in the literature wherein the guanidyl $-NH_2$ group is functionalized with alkylphenyl groups, wherein the phenyl is further substituted with halogen, methyl or amino groups. Such compounds, for example, are known from US 4,085,211 (Cragoe, Jr. et al), which describes compounds of the following structures:



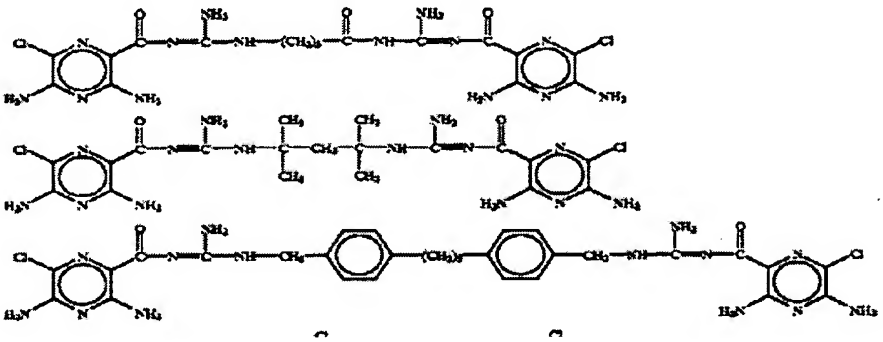
and

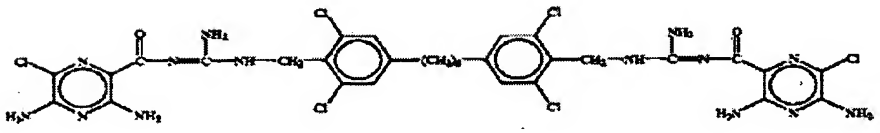


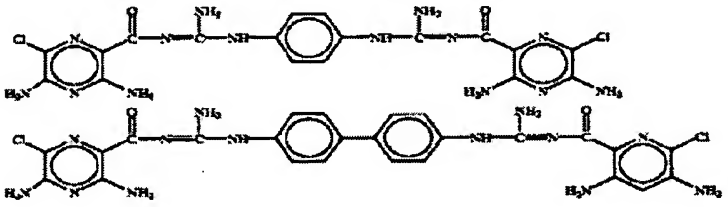
One such alkylphenyl-guanidine functionalized derivative of amiloride, wherein the phenyl group is substituted with carboxylic acid group was reported in Kleyman et al, "Distinct epitopes on amiloride. II. Variably restricted epitopes defined by monoclonal anti-amiloride antibodies" American Journal of Physiology, vol. 260(2, Pt. 1), pages C271-C276 (1991). The compound has this structure:



US 6,475,509 (Boucher, Jr. et al) is pertinent for its disclosure of *bis*-amiloride compounds having the following structural formulae, none of which is within the scope of any of the presently allowed claims:







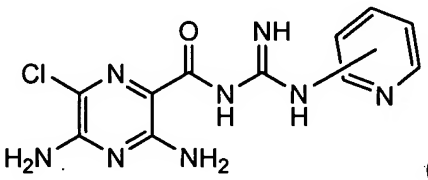
Another particularly pertinent disclosure is Velly et al, "Effects of amiloride and its analogues on [3H]batrachotoxinin-A 20-α benzoate binding, [3H]tetracaine binding and 22 Na influx" European Journal of Pharmacology, vol. 149, no- 1-2, 1988, pages 97-105. Velly et al reports several derivatives of amiloride which are not disclosed in any of the other references, cited hereinabove. Structures of these compounds are shown in Table I on

page 99 of the reference. Velley et al teach a number of alkylphenyl-guanidine derivatives along the lines of the above-cited Kleyman et al article.

The compounds according to the allowed claims are different from all of those described in the preceding, most notably because the derivitizations of the guanidyl $-NH_2$ group is with a pyridine ring-containing element. At least one of the variables "Q" in the formula (A) specified in instant claim 82 must be a nitrogen atom, providing for a pyridine ring. This pyridine ring must be further substituted with at least one hydroxy group -OH.

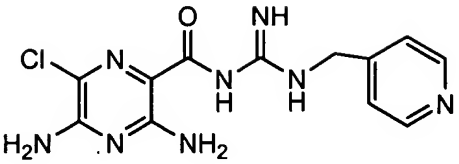
Amiloride derivatives, similar to those described in the preceding, except the phenyl ring is a pyridine ring (like the compounds according to the present invention) are known from the prior art.

US 4,264,406 (Cragoe, Jr. et al) teaches a series of heterocyclically substituted amiloride derivatives, wherein the guanidyl $-NH_2$ is bonded to a heterocyclic ring of varying identities. In the examples is described two compounds following structural formula shown:

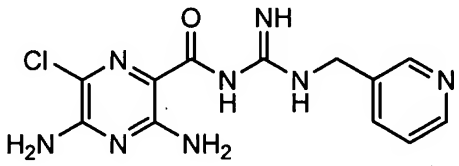


(where pyridyl is bonded *via* 2- and 3-positions)

Cocks et al, "Amiloride analogues cause endothelium-dependent relaxation in the canine coronary artery *in vitro*; possible role of Na^+/Ca^{2+} exchange" British Journal of Pharmacology, vol. 95(1), pages 67-76 (1988) reports a compound represented by the diagram below:



A structural isomer of the compound depicted in the immediately preceding paragraph, wherein the pyridine ring is bonded *via* the 3-position instead of the 4-position, whose structure is shown below, is disclose in many patents and scientific journal articles, by many inventors and researchers:



This compound is disclosed in US 3,573,306 (Shepard et al), US 3,539,569 (Tull and Pollack), US 3,472,848 (Cragoe, Jr. et al), and in many others.

Though pyridylmethyl substituted amiloride derivatives like those described herein are known, none of the references disclosing such compounds actually describes any compound embraced by the instant claims, and none provides any suggestion to place a hydroxyl substitution on the pyridine ring. It is noted also that formula (I) according to instant claim 82 also includes variable identities in "X," "Y," "R^2," "R^1" and the linker moiety in (A) which provides for much more than only derivatives of amiloride, which are those compounds according to formula (I) wherein the pyrazine ring is 3,5-diamino-6-chloro-substituted.

Applicant has been granted two other U.S. patents related to the instant application, wherein the "Q" containing ring is a pyridine ring – US 6,858,615 and US 6,995,160. Upon review of the claims in those patents, it is apparent that there is no overlap between the

compounds claimed therein and those compounds according to the instant claims, because the definitions for the variable R^5 are different.

Insofar as applicant's other issued U.S. patents disclosing and claiming sodium channel blocker compounds based on the same core amiloride motif, none of those patents poses any double patenting issues with respect to the instant claims, although the language of the method claims in these issued patents is the same, the compounds with which the methods are practiced are different. There is no overlap between any of the instantly claimed subject matter and subject matter claimed in applicant's other patents in the present series.

These issued patents are:

US 6,858,614, US 6,828,615, US 6,903,105, US 6,995,160, US 7,026,325, US 7,030,117 and US 7,064,129.

The therapeutic utility of the compounds according to the instant claims is mediated by sodium channel blockade due to the compounds' sodium channel blocking effect. Blockade of sodium channels causes an increase in mucous clearance and increased hydration. A representative number of diseases and conditions treated by the pharmacological effect of blocking sodium channels is set out at pages 9-11 of the instant specification.

Claim 117 is drawn to a multiple active ingredient composition comprising a compound according to instant claim 82 and a bronchodilator. One of ordinary skill in the art was well aware of what compounds the term "bronchodilator" embraced at the time the invention was made.

Claim 116 is drawn to a multiple active ingredient composition comprising a compound according to instant claim 82 and a P2Y2 agonist. As evidence that one of ordinary skill in the art understood what types of therapeutic agents "P2Y2 receptor agonist" was contemplative of at the time the invention was made, the examiner would cite:

> Kellerman, D. "P2Y2 Receptor Agonists. A New Class of Medication Targeted at Improved Mucociliary Clearance" Chest, vol. 121(5), supplement, pages 201S-205S.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday to Friday from 5:45am to 2:15pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Zachary C. Tucker
Primary Examiner
Art Unit 1624